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Physical Activity and Healthy Ageing: A Systematic Review and Meta-analysis of longitudinal cohort studies

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Highlights:

- Higher levels of physical activity increase the odds of healthy ageing by 39%
- High heterogeneity in the definition and measurement of healthy ageing
- High heterogeneity in the measurement of physical activity; misconception between the terms of physical activity and exercise
- Limited research in low and middle income countries

Abstract (250)

Background: Older people constitute a significant proportion of the total population and their number is projected to increase by more than half by 2050. This increasing probability of late survival comes with considerable individual, economic and social impact. Physical activity (PA) can influence the ageing process but the specific relationship with healthy ageing (HA) is unclear.

Methods: We conducted a systematic review and meta-analysis of longitudinal studies examining the associations of PA with HA. Studies were identified from a systematic search across major electronic databases from inception as January 2017. Random-effect meta-analysis was performed to calculate a pooled effect size (ES) and 95% CIs. Studies were assessed for methodological quality.

Results: Overall, 23 studies were identified including 174,114 participants (30% men) with age ranges from 20 to 87 years old. There was considerable heterogeneity in the definition and measurement of HA and PA. Most of the identified studies reported a significant positive association of PA with HA, six reported a non-significant. Meta-analysis revealed that PA is positively associated with HA (ES: 1.39, 95% CI=1.23-1.57, n=17) even if adjusted for publication bias (ES: 1.27, 95% CI=1.11-1.45, n=20).

Conclusions: There is consistent evidence from longitudinal observational studies that PA is positively associated with HA, regardless of definition and measurement. Future research should focus on the implementation of a single metric of HA, on the use of objective measures for PA assessment and on a full-range of confounding adjustment. In addition, our research indicated the limited research on ageing in low-and-middle income countries.

Keywords: healthy ageing, successful ageing, physical activity, exercise, meta-analysis.

1. INTRODUCTION

Physical activity refers to any bodily movement that is produced by the skeletal muscles and results in energy expenditure; whilst exercise is a subset of physical activity since it is a planned, structured and repetitive process that aims to maintain and improve physical fitness (Caspersen et al., 1985). There is a growing body of interest that physical activity and exercise confer favourable health outcomes across the lifespan. Based on a recent systematic review of longitudinal cohorts, physical activity is associated with a reduction in obesity, weight gain, coronary heart diseases (CHD), type II diabetes mellitus and the age-related diseases of dementia and Alzheimer's disease (Reiner et al., 2013). In addition, physical activity has been consistently linked to decreased all-cause mortality rates, probability of late survival (Blair and Brodney, 1999), (Benetos et al., 2005), (Bembom et al., 2009), good health and function during older age (Yates et al, 2009) as well as to cognitive performance (Newson and Kemps, 2006). Conversely, sedentary behaviour, defined as any waking behaviour characterised by an energy expenditure less or equal than 1.5 metabolic equivalents (METs) whilst in a sitting or reclining posture (Networ, 2012), is associated with an unfavourable biomarker profile in older age (Wirth et al., 2016). Finally, a large meta-analysis indicated that prolonged sedentary time is associated with all-cause mortality, cardiovascular disease (CVD) incidence and mortality, type II diabetes incidence and cancer (Biswas et al., 2015).

Based on recent systematic reviews, exercise has been characterised as an evidence-based treatment for depression (Schuch et al., 2016) and as a resource of improvement of cognition, working memory and attention to detail for patients with schizophrenia (Firth et al., 2016). A decreased risk of functional limitation and disability is also observed in older people who participate in regular aerobic activities (Nusselder et al. 2008), (Paterson and Warburton, 2010). Engaging in physical activities so as to promote and maintain good health is recommended across the whole life-span (Haskell et al., 2007), (Janssen and LeBlanc, 2010). Besides the amplified evidence of the benefits of a physically active lifestyle, physical inactivity, together with alcohol and exposure to tobacco smoking, remain the major behavioural burdens worldwide, based on findings from the Global Burden of Disease (IHME, 2016).

Chronic non-communicable diseases figure amongst the primary contributors of the disease burden arising from behavioural risk factors, and people 60 years old and over are accounted for almost 25% of it (Prince et al., 2015). Furthermore, the world is experiencing a considerable increase in the older population, with more than 900 million people aged 60 and over currently living worldwide, and this number is projected to grow by 56% between 2015 and 2030 (United Nations, 2015). Living longer does not necessarily entail experiencing better health than previous generations (Beard et al., 2016), as this demographic transition is associated with an increase in chronic physical illnesses. CVD constitutes the leading cause of death in the United States of America and is responsible for almost one fifth of national health expenditures; these costs are projected to increase by more than 60% in 2030 (Heidenreich et al., 2011). Globally, mortality rates due to communicable, maternal neonatal and national diseases have declined, but in contrast the disease burden has been shifted to non-communicable diseases and this burden is likely to continue expanding (IHME, 2016). This can ultimately lead to higher health and social care costs. The rising healthcare costs have led governments and societies to start developing policies for healthy ageing, aiming not only at prolonging the duration of later life, but as well as to improving it (Hung et al., 2010).

In the most recent World Health Organization ageing report, healthy ageing was defined as the process of developing and maintaining the functional ability that enables wellbeing in older age (Beard et al., 2016). Even though there is a lack of consensus regarding the definition of healthy ageing (Depp and Jeste, 2006), the scientific community have tried to identify those factors that will allow individuals to age physically and mentally healthily. There are several modifiable factors which could reduce premature death, prevent morbidity and disability, and improve the quality of life and well-being (Action plan for implementation of the European strategy for the prevention and control of Noncommunicable diseases, 2012-2016, 2012) and hence contribute to the increase of the likelihood of a healthy ageing. In addition, compression of morbidity in later life could be achieved by successful interventions early in life, as many disabilities are the result of a hazardous accumulated lifestyle (Chatterji et al., 2015). In a review published over a decade ago, physical activity, smoking and alcohol use were identified as the most frequent behavioural determinants of healthy ageing (Peel et al., 2005).

The aim of this systematic review and meta-analysis is to examine and synthesise the associations of physical activity and healthy ageing in longitudinal cohorts of community based adults.

2. METHODS

This systematic review was registered in the PROSPERO international database of prospectively registered systematic reviews (protocol number: CRD42016038130) and written in accordance with PRISMA and MOOSE statement for reporting systematic reviews and meta-analyses (Shamseer et al., 2015), (Stroup et al., 2000). In the supplementary file we have attached a MOOSE checklist. As part of a larger body of work considering modifiable lifestyle factors and healthy ageing, we originally planned to carry out a review focusing on: physical activity, smoking and alcohol consumption. The current systematic review specifically focuses on physical activity and healthy ageing outcome since a sufficient amount of literature was identified on this topic alone.

2.1 Search Strategy

MEDLINE (PubMed/PubMed Central interface), EMBASE (OVID interface), Psychinfo (OVID interface) and CENTRAL (Cochrane Central Register of Controlled Trials) were searched from inception up to April 2016. Searching methodology included any related term or synonym to healthy ageing and text word related to physical activity, smoking and alcohol consumption. Details for the searching technique are available in the Appendix A. Other relevant systematic reviews of healthy ageing and reference lists of the eligible studies have also been searched. Finally, a second search was performed in January 2017 so as to include studies that were recently published.

An EndNote (ENDNOTE X7, Thomson Reuters) library was created so as to store all the studies retrieved in the electronic databases. Using EndNote's auto-deduplication function, duplicate citations were removed. Since auto-deduplication is thought to be only partially successful (Qi et al., 2013), the remaining duplicates were identified by hand-searching techniques. To do this, references were alphabetically ordered according to the first authors' names and thereafter according to their titles. The retrieved papers were examined by two different reviewers (C.D., C.K.) in two stages; first the relevance of the study was judged by the title and the abstract and if the eligibility of the study remained unclear, the full text was read. At the end of this procedure, any disagreement was solved by discussion between the two reviewers. In case that an agreement could not be achieved, eligibility of the study was judged by discussion with a third senior researcher (A.M.P.). In case that full text could not be retrieved, the corresponding author of the paper was contacted via e-mail.

2.2 Study Inclusion & Exclusion

Eligible studies had to fulfil the following criteria: i. be published in an electronic journal article; ii. constitute an original peer-reviewed longitudinal study; and iii. report any kind of longitudinal association between physical activity and healthy ageing. Regarding physical activity and exercise, both terms were included in our research, since even if they describe different concepts, they are often used as synonyms (Caspersen et al., 1985). However, for the remainder of the manuscript, we will use the term physical activity to encompass both concepts. To be considered an eligible study, physical activity had to be measured either by self-reported questionnaires and/or by more objective tools, such as accelerometers or pedometers. The primary outcome of this review was health status measured by healthy ageing, and any other term related to it (e.g. successful ageing, active ageing, healthy survival etc.). Studies whose primary goal was the examination of a different determinant/factor but included the aforementioned factors as covariates or as latent factors were also included. Due to the heterogeneity of the healthy ageing definition, studies reporting the latter as multiple outcomes or based solely on self-report were excluded. Studies that included cohorts that were institutionalised or hospitalised, and animal studies, were also excluded. No language restriction was applied.

2.3 Data Extraction

Data from each study were independently extracted by the two reviewers C.D. and C.K. and a random sample of them was cross-checked by A.M.P. Setting/country of the study, data collection period, follow-up year, sample size, population, and baseline age information was recorded for each study. Definition and measurement of the healthy ageing outcome and of physical activity were also recorded, as well as the odds ratios (or any other related statistic) and the 95% confidence intervals (CI). Crude and the most adjusted odds ratios (OR) were extracted.

2.4 Role of the funding source

This project falls under the ATHLOS (Ageing Trajectories of Health: Longitudinal Opportunities and Synergies) project, funded by the European Union's Horizon 2020 Research and Innovation Programme under grant agreement number 63531. The sponsor of the current systematic review had no participation in the study design, data extraction, data interpretation, or writing of this paper.

2.5 Quality Assessment

Quality assessment of the eligible studies was performed by using the Quality in Prognosis Studies (QUIPS) tool. QUIPS evaluates six potential components of bias: inclusion, attrition, prognostic factor measurement, confounders, outcome measurement, and analysis and reporting, (Hayden et al., 2013). During the application of the QUIPS tool, the following alterations were done: physical activity was considered as the only prognostic factor and all other variables, used as explanatory variables of the model, were considered as confounders. Exception to this rule were studies that explicitly stated, even in their title, that the association of some other factor with healthy ageing was examined. In this case, the specific factor together with physical activity were evaluated as prognostic factors. Moreover, since only longitudinal studies were considered, attrition was expected. Where the attrition rate was high, authors' explanations were sought so as to evaluate the risk of bias within these studies. Finally, the reliability of statistical models was evaluated according to the data presented; for example papers that included results solely for the statistical significant factors were judged with caution. (Implementation of QUIPS tool is provided in the Appendix B).

2.6 Statistical Analysis

In the meta-analysis we aimed to: i) establish the effects of physical activity on healthy ageing and extract a pooled effect size (ES) estimate by comparing participants who belonged to the highest versus the lowest reported physical activity group, (e.g. high vs non-exerciser (Burke et al., 2001), vigorous vs low (Gureje et al., 2014), active vs inactive (Hodge, O'Dea et al., 2013)), ii) investigate, via sensitivity and subgroup analyses, the magnitude of the effects for the association between physical activity and healthy ageing, considering the following: study quality, baseline mean age, follow-up time, areas of information used for the definition of healthy ageing, measurement of physical activity or exercise and definition of physical activity, iii) identify any potential modifiers through meta-regression analyses and iv) assess the influence of publication bias on the reported effects.

Due to the expected heterogeneity, random effects meta-analysis using the DerSimonian-Laird model was performed (DerSimonian and Laird, 1986). Among the considered studies, the following measures of association between healthy ageing and physical activity were found: OR, Risk Ratios (RR) (one study), Hazard Ratios (HR) (one study) and Proportion of Healthy/Successful Years (HY) (two studies) and their 95% CIs. Our pooled ES estimate is given by taking into account only studies reporting ORs, however we also calculated a pooled ES estimate for all reported statistics, by considering HR and RR as similar, to test the robustness of our estimate. All studies were included in the meta-analyses except one that reported the β coefficient of linear regression analysis (Palmore, 1979), one that did not report non statistically significant results (Terry et al., 2005), and one that provided β coefficient of a linear mixed model (Tampubolon, 2016).

Firstly, we computed a meta-analysis by considering all the studies reporting ORs and by including the results of the most adjusted model. If a study reported different results per men and women both results were included, except in cases (e.g. Gureje et al., 2014) where a result for the mixed population was also provided. We subsequently conducted sensitivity analyses by computing the effect of physical activity on healthy ageing in studies with low risk of bias and by considering the results of the unadjusted models (when these were available). To understand part of the observed heterogeneity we also performed subgroup analyses. Subgroup analyses were performed by creating the following indicator variables: (i) biomedical model; this variable indicated if the following areas of information were included in the definition of healthy ageing: physical performance, diseases and mental health status, (ii) physical activity binary; this variable indicated if physical activity was measured as a binary variable (physical active or inactive) or more levels of physical activity were taken into account (for example low, medium, high), (iii) physical activity & exercise; this variable indicated if in the individual study physical activity or exercise was measured (Appendix C), (iv) age; this variable indicated if the baseline mean age of the participants was below or above 65 years old, (v) follow-up; this variable indicated if the follow-up of the study was less than or equal to, or more than 10 years.

Further, we conducted meta-regression analyses to investigate potential sources of heterogeneity and modifiers. We examined baseline mean age, measurement of physical activity and healthy ageing, and follow-up time. Heterogeneity was assessed with the Cochran Q and I^2 statistics for each analysis (Higgins et al., 2003). Publication bias (Sterne et al., 2001) was assessed graphically with contour-enhanced funnel plots (Newton and Cox, 2009) which show if studies are missing only from areas of low statistical significance; if they do then any asymmetry is very likely to be caused from publication bias (Peters et al., 2008). We also assessed publication bias with Begg-Mazumdar Kendall's tau (Begg and Mazumdar, 1994) and Egger bias test (Egger et al., 1997). Finally, a trim-and-fill adjusted analysis was conducted (Duval and Tweedie, 2000) so as to adjust for potential publication bias. All analyses were performed using STATA 14 IC statistical software.

3. RESULTS

3.1 Included Studies

6,706 articles were initially identified from the databases plus 30 from other sources. After removal of duplicates and exclusion of papers that were abstracts, conference papers, cross-sectional studies or animal studies, 73 were selected for full-text review. 42 were excluded after the full text review and 23 were included in the final review of this report. In Fig.1, the PRISMA flow chart depicts the exact process. Across the 23 eligible studies, there were 174,114 participants (almost 30% men), with sample size ranging from 155 to 68,153. Ten studies took place in USA, four in Australia and England, two in China and in Canada, and one study took place in Nigeria. Baseline mean age ranges from 20 to 87 years old and follow-up time from two years until death (>60 years old). Only five out of the 23 focused solely on sub-groups of men or women. Details of the included studies are presented in Table 1.

Healthy ageing, and any other term used as a synonym, was defined by including various areas of information to each study. These were grouped in the following categories: survival to a specific age or during follow-up, health status (either self-reported or measured by specific questionnaires), physical performance (including information regarding mobility, disabilities and/or difficulties in activities of daily living (ADL) and instrumental activities of daily living (iADL)), diseases (including chronic diseases and cancer), mental health and cognition status, subjective measurements of the participants (life satisfaction, happiness, and pain) and other (anthropometric measurements, personal assistance, social support). Most of the studies (19 out of 23) included physical performance to define healthy ageing and more than half of them (13 out of 23) included information regarding diseases and mental health. Survival to a specific age was also an area often found in the definition of healthy ageing, whereas health status and subjective measurements were not so often included. (Appendix D presents the areas of information that were present in the definition of healthy ageing per study).

Almeida and colleagues (2013) reported that engaging in a physically active lifestyle increases the likelihood of men aged 65-83 years to remain alive and free of functional or mental impairments after 10-13 years of follow up by 1.6-fold. Results of the same direction were also reported by Andrews et al. (2002), Burke et al. (2001) and Britton et al. (2008). The latter reported that the odds of healthy ageing for men and women, who engage in vigorous physical activity during midlife, were double compared to those that do none or mild exercise. Gu et al. (2009) revealed that elders who do regular exercise could improve the odds of healthy survival by 30% than those who do not, whereas Hamer et al. (2013) by using data from the English Longitudinal Study of Ageing (ELSA) found that people that did moderate or vigorous activity were 3.1-fold and 4.3-fold more likely to be healthy agers. Increased odds of healthy ageing were also reported to Hodge, English et al. (2013), to Hodge, O'Dea et al. (2013) and to LaCroix (2016). The only non-English study was that of Li et al. (2009) where regular exercise was also related to increased odds of successful ageing. Newman et al. (2003), Palmore (1979), Sabia et al. (2012), Shields & Martel (2006), Vaillant & Mukamal (2001), and Sun et al. (2010) also reported a positive association between physical activity and the odds of successful survival. Participants with higher levels of physical activity also reported higher levels of healthy ageing phenotype (Tampubolon et al., 2016). Only six out of the 23 studies report no association between healthy ageing and physical activity (Bell et al., 2014), (Ford et al, 2000), (Gureje et al., 2014), (Kaplan et al, 2008), (Pruchno & Wilson-Genderson, 2014) and (Terry et al. 2005). No study reported a negative association. In Table 2, the analytical results of this systematic review are presented. Statistics per study are provided for every category of the physical activity variable as well as for the most and least adjusted models. In addition, the confounders used for the final adjustment of the models are provided.

3.2 Quality Assessment

Of the 23 studies, two were evaluated as having high risk of bias, five as moderate and 16 as having low. In aggregate, the quality of the included studies was high. Attrition and confounder measurement issues were those that reported the majority of moderate and high bias. Specifically, 14 out of 23 studies reported moderate or high risk of bias regarding the fact that the population lost to follow-up may be associated with key characteristics that could influence the observed relationship between the outcome and the factors. The same was also observed for the confounders' domain, where 16 out of 23 studies were characterised as having moderate risk of bias, meaning that important confounders may have not been appropriately accounted in the final model. The analytical results of the quality assessment are provided in the Appendix B.

3.3 Meta-analysis

3.3.1 Main results

Data pooled from the studies showed a significant positive association between physical activity and healthy ageing (ES=1.39, 95% CI 1.23-1.57, $p<0.001$, Q=84.73, I^2=81.1%, $p<0.001$). Our graph did not provide evidence for publication bias (Appendix E). In addition, both Begg-Mazumdar Kendall's Tau ($p>0.05$) and the Egger Test (bias= 1.50, 95% CI: -0.51 to 3.51, p=0.133) did not provide evidence for publication bias. However, we still adjusted our pooled estimate with the trim-and-fill algorithm and the association remained positive and significant as decided a priori (ES(filled studies)=1.27, 95% CI 1.11-1.45, 3 filled studies). Analytical results are provided in Table 3.

3.3.2 Sensitivity and Subgroup analysis

Sensitivity and subgroup analyses were all adjusted for publication bias by using the trim-and-fill algorithm; the effect of physical activity on healthy ageing was slightly overestimated in most of them. However, the significant positive association of physical activity on healthy ageing remained after adjustment in the majority of analyses (Table 3). The pooled ES estimate increased when we took into account only studies with low risk of bias (1.43 vs 1.39) and when we considered the least adjusted models (1.51 vs 1.39) but it did not vary when we considered all the reported statistics (1.38 vs 1.39). The odds of healthy ageing for people engaging in physical activity were higher when studies included information on physical performance, diseases and mental status in their definition of healthy ageing (1.61 vs 1.14) and in those where physical activity was not recorded as a binary variable (1.68 vs 1.26). Younger participants exhibited higher pooled ES than older participants (1.64 vs 1.14) whereas no difference was revealed among studies which had follow-up time more than 10 years and those with equal or less than 10 years (1.37 vs 1.39). Studies that measured exercise reported a lower pooled ES compared to studies that measured physical activity (1.20 vs 1.46). However, this finding did not hold when we also took into account the follow-up time. More specifically, when examining studies with follow-up of more than 10 years the pooled ES of studies measuring exercise was 1.88 (95%CI: 1.39-2.55) whereas the pooled ES of studies measuring physical activity was 1.33 (95%CI: 1.19-1.47) (results are provided upon request).

3.3.3 Meta-regression

In order to understand the relatively high heterogeneity, meta-regression analyses were performed on the natural logarithm of the ES. Baseline mean age and the variable indicating the areas of information in the definition of healthy ageing emerged as significant modifiers. Studies with lower baseline mean age and studies that defined healthy ageing with a biomedical model produced higher positive impact. The variable indicating if studies measured physical activity or exercise was not statistically significant. Follow-up time was also not statistically significant. The full meta-regression data is presented in Table 4. Pooled ES were also produced by omitting one-by-one the included studies. The pooled ES ranged from 1.30 to 1.42 and the 95% CI ranged from 1.18 to 1.63 (Appendix F).

4. DISCUSSION

To our knowledge, this systematic review is the first to examine the association between physical activity and healthy ageing, by performing a meta-analysis so as to produce a pooled effect estimate and adjusting for publication bias. Our study highlights the positive impact of physical activity on the healthy ageing process. More specifically, our data suggest that in the majority of studies, when participants engaged in physical activity their odds of living a healthy life in an older age were increased compared to participants that were physically less active or inactive (Table 2). From our review it also becomes evident that the majority of the studies have been implemented in high-income countries. Thus, in accordance with a previous study (Chatterji, 2015), the current investigation ascertains the present limited research on ageing in low and middle income countries (LMICs). Nevertheless, estimations have shown that the population growth in developing countries will be more rapid than the one experienced by developed countries and that by 2050 80% of the people aged 60 years and over will live in a LMIC (WHO, 2016).

Furthermore, we tried to synthesise our results by producing a pooled effect estimate despite the quite high heterogeneity (I^2=81.1%). However, rarely are studies identical replications of one another, so including studies that are diverse in methodology, measures, and sample within our meta-analysis exhibits the advantage of improving the generalisability of our conclusions (Rosenthal & DiMatteo, 2001). MOOSE guidelines also recommend the investigation of high heterogeneity by subgroup and meta-regression analysis (Stroup et al., 2000). The pooled estimate was 1.39 (95%CI: 1.23 - 1.57) and the positive association held even when its robustness was tested by performing sensitivity and subgroup analyses. From statistical tests (Begg-Mazumdar Kendall's Tau and Egger Bias test), graphical examination (funnel plot-Appendix E) and the application of the trim-and-fill algorithm we conclude that our data did not show significant evidence for publication bias.

Nevertheless, by performing subgroup analyses, we found that the different metrics of physical activity influenced the final outcome. More specifically, when physical activity was defined as a binary variable (i.e. such an approach would not take into account the level or intensity of the activity), the associations were smaller compared to studies in which different levels of activity were taken into account. However, this finding could have been influenced by the studies comparing high levels of physical activity to lower levels (i.e. vigorous vs low in Gureje et al. (2014)). In addition, our review revealed a misconception regarding the classification of the terms physical activity and exercise. We tried to categorise our studies, so as to explain more of the underlying heterogeneity however, it was not always easy to understand what actually had been measured in the individual considered studies. A higher association was observed between healthy ageing and studies measuring PA than studies measuring exercise, but the opposite result was indicated when only studies of more than 10 year follow-up time were considered. When adjusting the physical activity related subgroup analyses with the trim-and-fill algorithm, associations remained positive but not statistically significant in a 95% CI. Our review indicated that future studies should exhibit a more straightforward definition and measurement of physical activity.

Differences were also identified when we examined studies based on the areas of information included in the definition of healthy ageing. Studies that defined the latter by including information on physical performance, diseases and mental status present increased OR for physically active participants. Based on a systematic review of healthy ageing, to date there is neither a unanimous definition nor a standardised metric of it; in addition, there is not an agreed term to use, with 'healthy ageing', 'successful ageing', 'productive ageing' or/and 'optimal ageing' all being used as synonyms (Depp & Jeste, 2006). Our review also confirms the lack of consensus metric and of a unanimous term. Healthy ageing, successful ageing, healthy years, healthy survivors, healthy survival, overall good health, exceptional survival, positive ageing, relatively healthy, thrivers were the terms that we found in our studies. Hence, it is highly recommended that future research should focus on a more standardised approach for the definition and the measurement of the healthy ageing outcome so as to facilitate comparisons among populations.

From our meta-regression analysis, we showed that baseline age and the definition of the metric of healthy ageing are significant modifiers. Physical activity definition was significant at a 10% level of significance (Table 4). Younger cohorts who engage in some form of physical activity were more likely to have a healthier life as they grow older. In addition, the areas of information included in the definition of healthy ageing influenced the final outcome. This finding comes in accordance with the comment of Phelan & Larson (2002) that predictors of successful ageing are influenced by the way the latter has been defined. We found a distinction between the biomedical models, which emphasise the absence of disease in parallel with good physical and mental functioning and the non-biomedical models. In the non-biomedical subgroup, socio-psychological models were also included which emphasise life satisfaction, social functioning and participation (Bowling and Dieppe, 2005). From our meta-regression we concluded that the biomedical models are more strongly associated with physical activity.

The precise mechanisms by which physical activity may promote healthy ageing are yet to be determined. However, this could be attributed in part to the favourable biomarkers profiles from physical activity such as reducing fat mass and adipose tissue inflammation (Woods et al., 2012). Furthermore, physical activity and exercise are known to prevent and reduce functional independence (Tak et al., 2013) as well as confer a protective influence on multiple non-communicable diseases. The latter may account for the positive impact of physical activity on healthy ageing.

4.1 Strengths and Limitations

The fact that this study has been done by independently double screening the initial results, taking into account previous systematic reviews in the field and the reference lists of the eligible papers allows a great amount of confidence that all relevant studies were included. Regarding the quality assessment of the studies, limited disagreement (less than 8%) among the six different domains per study was reached between the two reviewers, who independently assessed them, concluding that the QA tool was highly straightforward and did not allow great amount of misjudgement. Attrition rate and missing confounders in the final models were important factors for the quality of the studies; hence future studies should consider these important issues more thoroughly.

Nevertheless, the following limitations have to be taken into account. Each study was adjusted by using a different set of covariates, different follow-up time and attrition rate and all these could have contributed to the high heterogeneity observed in the meta-analysis and to the conclusions of our review. In addition, in all studies physical activity was measured by using self-reported questionnaires, which means that results were subject to potential bias. The use of more objective tools, such as an accelerometer, is highly recommended since self-reporting is also prone to recall bias with poor reliability and validity (Falck et al., 2015). There is also lack of consistency regarding the way frequency, intensity and duration of physical activity were reported. Similar problems are also mentioned in other systematic reviews of physical activity (Hamer & Chida, 2008), (Reiner et al., 2013). Furthermore, self-reported physical activity allows us to consider physical activity only during the time of examination whereas the monitoring of the physical activity level between questionnaire administrations and outcome is not measured. In this way we are not able to assess the impact of a continuous physical active lifestyle on healthy ageing. Finally, there is an ambiguity regarding the concepts that have actually been measured; physical activity or exercise. Hence, future research should focus on a more accurate definition and measurement of physical activity as well as the optimal dose of it for succeeding a healthy ageing.

4.2 Conclusion

In conclusion, engaging in physical activity increases the odds of maintaining our well-being in later life. This result is identified in both the majority of our primary studies and in our pooled effect estimate as well. Since our studies are all observational ones, a causal relationship between physical activity and healthy ageing should be argued with caution. From our research it becomes evident that there is an undisputable need to implement unanimous definitions and metrics of healthy ageing and physical activity across studies so as to ultimately make them comparable among different cohorts and waves. Implementation of a healthy ageing metric and more research in LMICs will also allow us to test measurement invariance hypotheses among different cultural settings, once these will be available. In addition, it will enable us to robustly estimate the point when a change in the ageing process occurs and to investigate which determinants trigger that change. ATHLOS project (http://athlosproject.eu/) aims to fill this knowledge gap by creating a harmonised dataset among different longitudinal cohorts, defining a unanimous healthy ageing index and common metrics of its determinants.

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REFERENCES

1. Action plan for implementation of the European strategy for the prevention and control of Noncommunicable diseases, 2012-2016 (2012) Copenhagen, Denmark: World Health Organization, Regional Office for Europe.
2. Almeida, O.P., Khan, K.M., Hankey, G.J., Yeap, B.B., Golledge, J. and Flicker, L. (2013) '150 minutes of vigorous physical activity per week predicts survival and successful ageing: A population-based 11-year longitudinal study of 12 201 older Australian men', British Journal of Sports Medicine, 48(3), pp. 220–225. doi: 10.1136/bjsports-2013-092814.
3. Andrews, G., Clark, M., & Luszcz, M. (2002). Successful aging in the Australian longitudinal study of aging: Applying the MacArthur model cross-nationally. Journal of Social Issues, 58(4), 749–765. doi:10.1111/1540-4560.00288.
4. Beard, J.R., Officer, A., de Carvalho, I.A., Sadana, R., Pot, A.M., Michel, J.-P., Lloyd-Sherlock, P., Epping-Jordan, J.E., Peeters, G.M.E.E.(g., Mahanani, W.R., Thiyagarajan, J.A. and Chatterji, S. (2016) 'The world report on ageing and health: A policy framework for healthy ageing', The Lancet, 387(10033), pp. 2145–2154. doi: 10.1016/s0140-6736(15)00516-4.
5. Begg, C.B. and Mazumdar, M. (1994) 'Operating characteristics of a rank correlation test for publication bias', Biometrics, 50(4), p. 1088. doi: 10.2307/2533446.
6. Bell, C.L., Chen, R., Masaki, K., Yee, P., He, Q., Grove, J., Donlon, T., Curb, J.D., Willcox, D.C., Poon, L.W. and Willcox, B.J. (2014) 'Late-life factors associated with healthy aging in older men', Journal of the American Geriatrics Society, 62(5), pp. 880–888. doi: 10.1111/jgs.12796.

7. Bembom, O., van der Laan, M., Haight, T. and Tager, I. (2009) 'Leisure-time physical activity and all-cause mortality in an elderly cohort', Epidemiology, 20(3), pp. 424–430. doi: 10.1097/ede.0b013e31819e3f28.

8. Benetos, A., Thomas, F., Bean, K.E., Pannier, B. and Guize, L. (2005) 'Role of modifiable risk factors in life expectancy in the elderly', Journal of Hypertension, 23(10), pp. 1803–1808. doi: 10.1097/01.hjh.0000179512.71018.40.

9. Biswas, A., Oh, P.I., Faulkner, G.E., Bajaj, R.R., Silver, M.A., Mitchell, M.S. and Alter, D.A. (2015) 'Sedentary time and its association with risk for disease incidence, mortality, and hospitalization in adults', Annals of Internal Medicine, 162(2), p. 123. doi: 10.7326/m14-1651.

10. Blair, S.N. and Brodney, S. (1999) 'Effects of physical inactivity and obesity on morbidity and mortality: Current evidence and research issues', Medicine & Science in Sports & Exercise, 31(Supplement 1), p. S646. doi: 10.1097/00005768-199911001-00025.

11. Bowling, A. and Dieppe, P. (2005) 'What is successful ageing and who should define it?', BMJ, 331(7531), pp. 1548–1551. doi: 10.1136/bmj.331.7531.1548.

12. Britton, A., Shipley, M., Singh-Manoux, A., & Marmot, M. G. (2008). Successful aging: The contribution of early-life and Midlife risk factors. Journal of the American Geriatrics Society, 56(6), 1098–1105. doi:10.1111/j.1532-5415.2008.01740.x.

13. Burke, G.L., Arnold, A.M., Bild, D.E., Cushman, M., Fried, L.P., Newman, A., Nunn, C. and Robbins, J. (2001) 'Factors associated with healthy aging: The cardiovascular health study', Journal of the American Geriatrics Society, 49(3), pp. 254–262. doi: 10.1046/j.1532-5415.2001.4930254.x.

14. Caspersen, C. J., Powell, K. E., & Christenson, G. M. (1985). Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. Public Health Reports, 100(2), 126–131.

15. Chatterji, S., Byles, J., Cutler, D., Seeman, T. and Verdes, E. (2015) 'Health, functioning, and disability in older adults—present status and future implications', The Lancet, 385(9967), pp. 563–575. doi: 10.1016/s0140-6736(14)61462-8.

16. Depp, C.A. and Jeste, D.V. (2006) 'Definitions and predictors of successful aging: A comprehensive review of larger quantitative studies', The American Journal of Geriatric Psychiatry, 14(1), pp. 6–20. doi: 10.1097/01.jgp.0000192501.03069.bc.

17. DerSimonian, R. and Laird, N. (1986) 'Meta-analysis in clinical trials', Controlled Clinical Trials, 7(3), pp. 177–188. doi: 10.1016/0197-2456(86)90046-2.

18. Duval, S., Tweedie, R., 2000. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics 56, 455-463.

19. Egger, M., Smith, G.D., Schneider, M. and Minder, C. (1997) 'Bias in meta-analysis detected by a simple, graphical test', BMJ, 315(7109), pp. 629–634. doi: 10.1136/bmj.315.7109.629.

20. Falck, R.S., McDonald, S.M., Beets, M.W. and Brazendale, K. (2015) 'Measurement of physical activity in older adult interventions: A systematic review', British Journal of Sports Medicine, , pp. 2014–94413. doi: 10.1136/bjsports-2014-094413.

21. Firth, J., Stubbs, B., Rosenbaum, S., Vancampfort, D., Malchow, B., Schuch, F., Elliott, R., Nuechterlein, K.H. and Yung, A.R. (2016) 'Aerobic exercise improves cognitive functioning in people with schizophrenia: A systematic review and Meta-Analysis', Schizophrenia Bulletin, , p. sbw115. doi: 10.1093/schbul/sbw115.

22. Ford, A. B., Haug, M. R., Stange, K. C., Gaines, A. D., Noelker, L. S., & Jones, P. K. (2000). Sustained personal autonomy: A measure of successful aging. Journal of Aging and Health, 12(4), 470–489. doi:10.1177/089826430001200402.

23. Gu, D., Zhang, Z., & Zeng, Y. (2009). Access to healthcare services makes a difference in healthy longevity among older Chinese adults. Social Science & Medicine, 68(2), 210–219. doi:10.1016/j.socscimed.2008.10.025.

24. Gureje, O., Oladeji, B. D., Abiona, T., & Chatterji, S. (2014). Profile and determinants of successful aging in the Ibadan study of Ageing. Journal of the American Geriatrics Society, 62(5), 836–842. doi:10.1111/jgs.12802.

25. Hamer, M. and Chida, Y. (2008) ‘Physical activity and risk of neurodegenerative disease: A systematic review of prospective evidence’, Psychological Medicine, 39(01), p. 3. doi: 10.1017/s0033291708003681.

26. Hamer, M., Lavoie, K. L., & Bacon, S. L. (2013). Taking up physical activity in later life and healthy ageing: The English longitudinal study of ageing. British Journal of Sports Medicine, 48(3), 239–243. doi:10.1136/bjsports-2013-092993.

27. Haskell, W.L., Lee, I.-M., Pate, R.R., Powell, K.E., Blair, S.N., Franklin, B.A., Macera, C.A., Heath, G.W., Thomson, P.D. and Bauman, A. (2007) ‘Physical activity and public health’, Medicine & Science in Sports & Exercise, 39(8), pp. 1423–1434. doi: 10.1249/mss.0b013e3180616b27.

28. Hayden, J.A., van der Windt, D.A., Cartwright, J.L., Côté, P. and Bombardier, C. (2013) ‘Assessing bias in studies of Prognostic factors’, Annals of Internal Medicine, 158(4), p. 280. doi: 10.7326/0003-4819-158-4-201302190-00009.

29. Heidenreich, P.A., Trogdon, J.G., Khavjou, O.A., Butler, J., Dracup, K., Ezekowitz, M.D., Finkelstein, E.A., Hong, Y., Johnston, S.C., Khera, A., Lloyd-Jones, D.M., Nelson, S.A., Nichol, G., Orenstein, D., Wilson, P.W.F. and Woo, Y.J. (2011) 'Forecasting the future of cardiovascular disease in the United States: A policy statement from the American heart association', Circulation, 123(8), pp. 933–944. doi: 10.1161/cir.0b013e31820a55f5.

30. Higgins, J.P.T., Thompson, S.G., Deeks, J.J. and Altman, D.G. (2003) 'Measuring inconsistency in meta-analyses', BMJ, 327(7414), pp. 557–560. doi: 10.1136/bmj.327.7414.557.

31. Hodge, A. M., English, D. R., Giles, G. G., & Flicker, L. (2013). Social connectedness and predictors of successful ageing. Maturitas, 75(4), 361–366. doi:10.1016/j.maturitas.2013.05.002.

32. Hodge, A. M., O'Dea, K., English, D. R., Giles, G. G., & Flicker, L. (2013). Dietary patterns as predictors of successful ageing. The journal of nutrition, health & aging, 18(3), 221–227. doi:10.1007/s12603-013-0405-0.

33. Hung, L.-W., Kempen, G.I.J.M. and De Vries, N.K. (2010) 'Cross-cultural comparison between academic and lay views of healthy ageing: A literature review', Ageing and Society, 30(08), pp. 1373–1391. doi: 10.1017/s0144686x10000589.

34. Institute for Health Metrics and Evaluation (IHME). Rethinking Development and Health: Findings from the Global Burden of Disease Study. Seattle, WA: IHME, 2016.

35. Janssen, I. and LeBlanc, A.G. (2010) 'Systematic review of the health benefits of physical activity and fitness in school-aged children and youth', International Journal of Behavioral Nutrition and Physical Activity, 7(1), p. 40. doi: 10.1186/1479-5868-7-40.

36. Kaplan, M. S., Huguet, N., Orpana, H., Feeny, D., McFarland, B. H., & Ross, N. (2008). Prevalence and factors associated with thriving in older adulthood: A 10-Year population-based study. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences, 63(10), 1097–1104. doi:10.1093/gerona/63.10.1097.

37. LaCroix, A. Z., Rillamas-Sun, E., Woods, N. F., Weitlauf, J., Zaslavsky, O., Shih, R., LaMonte, M. J., Bird, C., Yano, E. M., LeBoff, M., Washington, D., Reiber, G. (2016). Aging well among women veterans compared with non-veterans in the women's health initiative. The Gerontologist, 56(Suppl 1), S14–S26. doi:10.1093/geront/gnv124.

38. Li, C., Zhang, M., He, Y., & Zhang, X. (2001). Impact of health behavior on successful aging: A 5-year follow-up study among community elderly. Chinese Mental Health Journal, 15, 324–326 (in Chinese).

39. Networ, S.B.R. (2012) 'Letter to the editor: Standardized use of the terms "sedentary" and "sedentary behaviours"', Applied Physiology, Nutrition, and Metabolism, 37(3), pp. 540–542. doi: 10.1139/h2012-024.

40. Newman AB, Arnold AM, Naydeck BL, et al. "Successful Aging": Effect of Subclinical Cardiovascular Disease. Arch Intern Med. 2003; 163(19):2315-2322. doi:10.1001/archinte.163.19.2315.

41. Newson, R.S. and Kemps, E.B. (2006) 'Cardiorespiratory fitness as a predictor of successful cognitive Ageing', Journal of Clinical and Experimental Neuropsychology, 28(6), pp. 949–967. doi: 10.1080/13803390591004356.

42. Newton, J.H. and Cox, N.J. (2009) Meta-analysis in Stata: An updated collection from the Stata journal. Edited by Tom M. Palmer and Jonathan A. C. Sterne. College Station, TX: Strata Press.

43. Nusselder, W.J., Looman, C.W.N., Franco, O.H., Peeters, A., Slingerland, A.S. and Mackenbach, J.P. (2008) 'The relation between non-occupational physical activity and years lived with and without disability', Journal of Epidemiology & Community Health, 62(9), pp. 823–828. doi: 10.1136/jech.2007.067165.

44. Palmore, E. (1979). Predictors of successful aging. The Gerontologist, 19(5 Part 1), 427–431. doi:10.1093/geront/19.5_part_1.427.

45. Paterson, D.H. and Warburton, D.E. (2010) 'Physical activity and functional limitations in older adults: A systematic review related to Canada's physical activity guidelines', International Journal of Behavioral Nutrition and Physical Activity, 7(1), p. 38. doi: 10.1186/1479-5868-7-38.

46. Peel, N.M., McClure, R.J. and Bartlett, H.P. (2005) 'Behavioral determinants of healthy aging1', American Journal of Preventive Medicine, 28(3), pp. 298–304. doi: 10.1016/j.amepre.2004.12.002.

47. Peters, J.L., Sutton, A.J., Jones, D.R., Abrams, K.R. and Rushton, L. (2008) 'Contour-enhanced meta-analysis funnel plots help distinguish publication bias from other causes of asymmetry', Journal of Clinical Epidemiology, 61(10), pp. 991–996. doi: 10.1016/j.jclinepi.2007.11.010.

48. Phelan EA, Larson EB: 'Successful aging'—where next? J Am Geriatr Soc 2002; 50:1306–1308.

49. Prince, M.J., Wu, F., Guo, Y., Gutierrez Robledo, L.M., O'Donnell, M., Sullivan, R. and Yusuf, S. (2015) 'The burden of disease in older people and implications for health policy and practice', The Lancet, 385(9967), pp. 549–562. doi: 10.1016/s0140-6736(14)61347-7.

50. Pruchno, R. A., & Wilson-Genderson, M. (2014). A longitudinal examination of the effects of early influences and Midlife characteristics on successful aging. The Journals of Gerontology Series B: Psychological Sciences and Social Sciences, 70(6), 850–859. doi:10.1093/geronb/gbu046.

51. Qi, X., Yang, M., Ren, W., Jia, J., Wang, J., Han, G. and Fan, D. (2013) 'Find duplicates among the PubMed, EMBASE, and Cochrane library databases in systematic review', PLoS ONE, 8(8), p. e71838. doi: 10.1371/journal.pone.0071838.

52. Reiner, M., Niermann, C., Jekauc, D. and Woll, A. (2013) 'Long-term health benefits of physical activity – a systematic review of longitudinal studies', BMC Public Health, 13(1), p. 813. doi: 10.1186/1471-2458-13-813.

53. Rosenthal, R. and DiMatteo, M.R. (2001) 'Meta-Analysis: Recent developments in quantitative methods for literature reviews', Annual Review of Psychology, 52(1), pp. 59–82. doi: 10.1146/annurev.psych.52.1.59.

54. Sabia, S., Singh-Manoux, A., Hagger-Johnson, G., Cambois, E., Brunner, E. J., & Kivimaki, M. (2012). Influence of individual and combined healthy behaviours on successful aging. Canadian Medical Association Journal, 184(18), 1985–1992. doi:10.1503/cmaj.121080.

55. Schuch, F.B., Vancampfort, D., Richards, J., Rosenbaum, S., Ward, P.B. and Stubbs, B. (2016) 'Exercise as a treatment for depression: A meta-analysis adjusting for publication bias', Journal of Psychiatric Research, 77, pp. 42–51. doi: 10.1016/j.jpsychires.2016.02.023.

56. Shamseer, L., Moher, D., Clarke, M., Ghersi, D., Liberati, A., Petticrew, M., Shekelle, P. and Stewart, L.A. (2015) 'Preferred reporting items for systematic review and meta-analysis

protocols (PRISMA-P) 2015: Elaboration and explanation', BMJ, 349(jan02 1), pp. g7647–g7647. doi: 10.1136/bmj.g7647.

57. Shields, M., & Martel, L. (2016, August 31). Healthy living among seniors. Retrieved August 31, 2016, http://www.statcan.gc.ca/access_acces/archive.action?loc=/pub/82-003-s/2005000/pdf/9086-eng.pdf&archive=1.

58. Sterne, J.A.C., Egger, M. and Smith, G.D. (2001) 'Systematic reviews in health care: Investigating and dealing with publication and other biases in meta-analysis', BMJ, 323(7304), pp. 101–105. doi: 10.1136/bmj.323.7304.101.

59. Stroup, D.F., Berlin, J.A., Morton, S.C., Olkin, I., Williamson, D.G., Rennie, D., Moher, D., Becker, B.J., Sipe, T.A. and Thacker, S.B. (2000) 'Meta-analysis of observational studies in Epidemiology', JAMA, 283(15), pp. 2008–2012. doi: 10.1001/jama.283.15.2008.

60. Sun, Q., Townsend, M. K., Okereke, O. I., Franco, O. H., Hu, F. B., & Grodstein, F. (2010). Physical activity at Midlife in relation to successful survival in women at age 70 years or older. Archives of Internal Medicine, 170(2), 194–201. doi:10.1001/archinternmed.2009.503.

61. Tak, E., Kuiper, R., Chorus, A. and Hopman-Rock, M. (2013) 'Prevention of onset and progression of basic ADL disability by physical activity in community dwelling older adults: A meta-analysis', Ageing Research Reviews, 12(1), pp. 329–338. doi: 10.1016/j.arr.2012.10.001.

62. Tampubolon, G. (2016). Trajectories of the healthy ageing phenotype among middle-aged and older Britons, 2004–2013. Maturitas, 88, 9–15. doi:10.1016/j.maturitas.2016.03.002.

63. Terry, D.F., Pencina, M.J., Vasan, R.S., Murabito, J.M., Wolf, P.A., Hayes, M.K., Levy, D., D'Agostino, R.B. and Benjamin, E.J. (2005) 'Cardiovascular risk factors predictive for survival and morbidity-free survival in the oldest-old Framingham heart study participants', Journal of the American Geriatrics Society, 53(11), pp. 1944–1950. doi: 10.1111/j.1532-5415.2005.00465.x.

64. United Nations, Department of Economic and Social Affairs, Population Division (2015) 'World Population Ageing 2015' (ST/ESA/SER.A/390).

65. Vaillant, G. E., & Mukamal, K. (2001). Successful aging. American Journal of Psychiatry, 158(6), 839–847. doi:10.1176/appi.ajp.158.6.839.

66. WHO (2016) Ageing and health. Available at: http://www.who.int/mediacentre/factsheets/fs404/en/ (Accessed: 8 November 2016).

67. Wirth, K., Klenk, J., Brefka, S., Dallmeier, D., Faehling, K., Figuls, M.R. i, Tully, M.A., Giné-Garriga, M., Caserotti, P., Salvà, A., Rothenbacher, D., Denkinger, M. and Stubbs, B. (2016) 'Biomarkers associated with sedentary behaviour in older adults: A systematic review', Ageing Research Reviews, . doi: 10.1016/j.arr.2016.12.002.

68. Woods, J. A., Wilund, K. R., Martin, S. A., & Kistler, B. M. (2012). Exercise, Inflammation and Aging. Aging and Disease, 3(1), 130–140.

69. Yates, L.B., Djoussé, L., Kurth, T., Buring, J.E. and Gaziano, J.M. (2009) 'Exceptional longevity in men: Modifiable factors associated with survival and function to age 90 years', Obstetrical & Gynecological Survey, 64(1), pp. 28–29. doi: 10.1097/01.ogx.0000340774.22542.88.

Fig.1. Flowchart of studies selection

PRISMA 2009 Flow Diagram

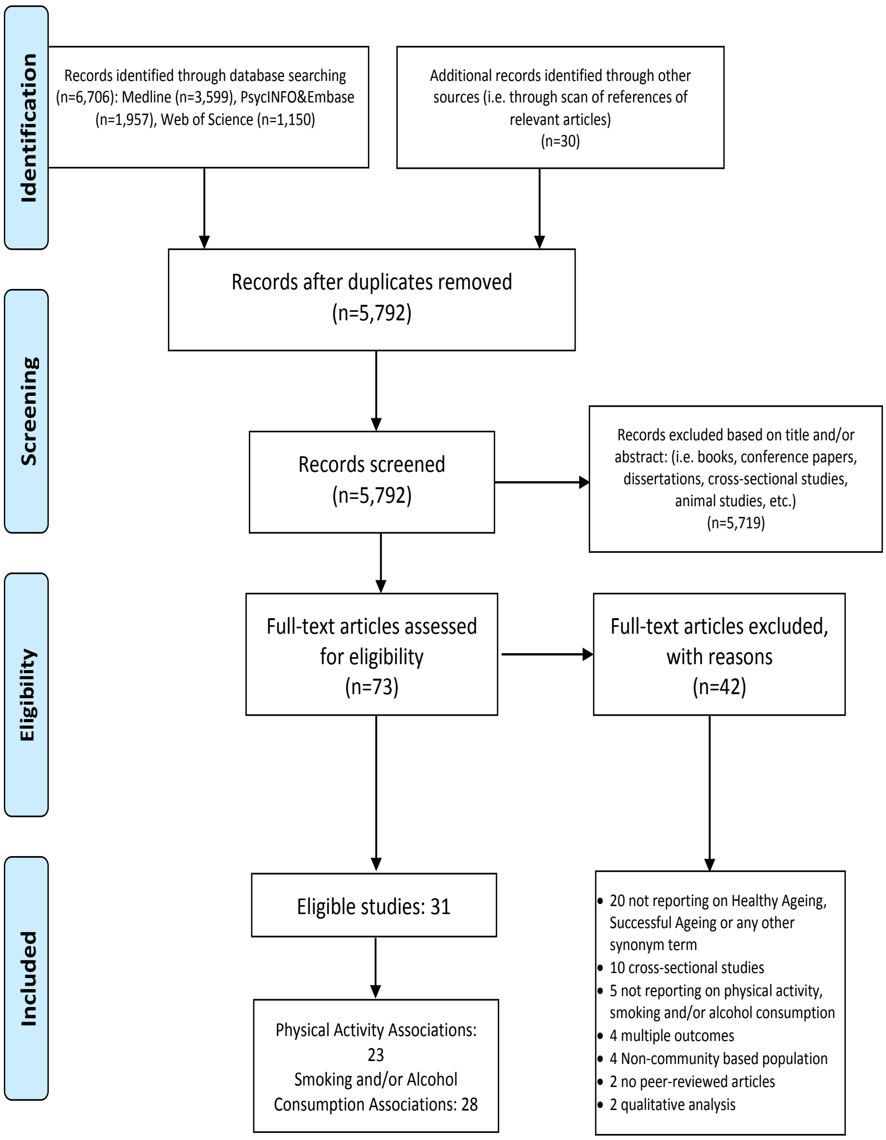

Fig.2. Meta-analysis of overall studies

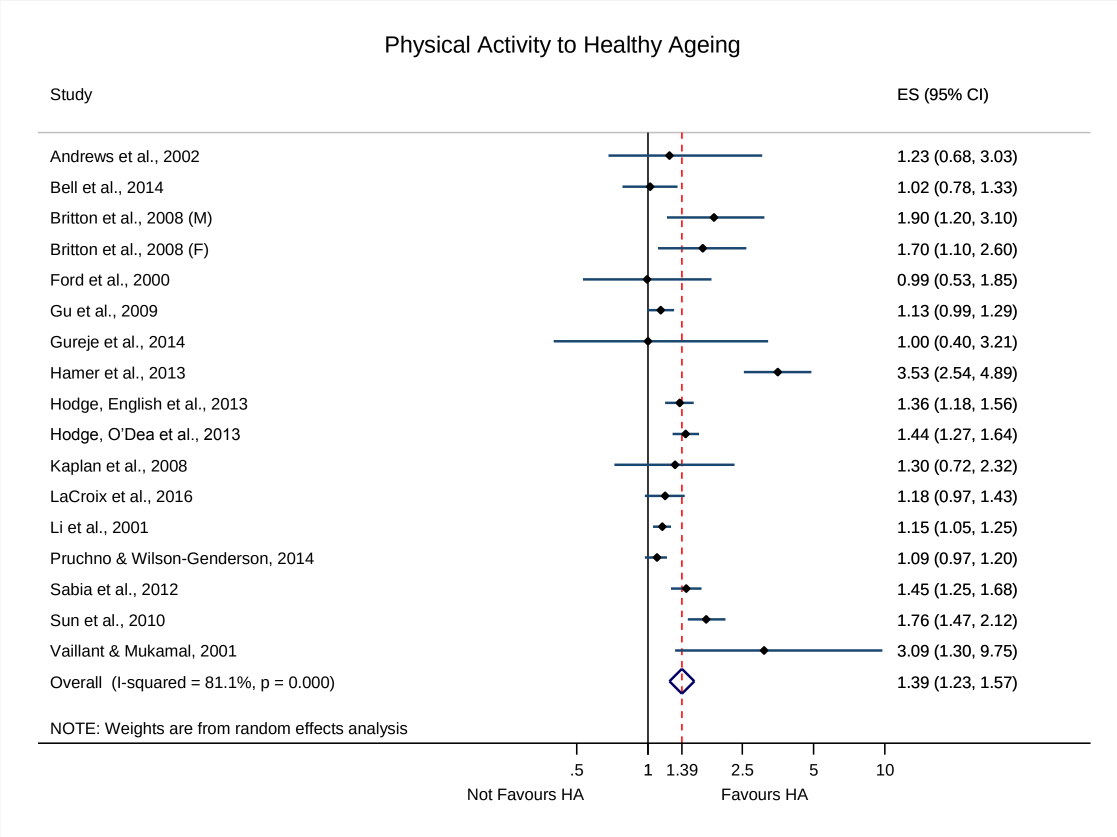

Table 1. Baseline characteristics of the eligible studies.

Authors	Country/ Panel	Data collection period	Follow-up (mean years, unless otherwise specified)	Sample Size	Gender	Baseline Age
Almeida et al., 2013	Australia/ Health In Men Study (HIMS)	1996 – 1998	9.8 - 12.6	12,201	100% men	65-83
Andrews et al., 2002	Australia/ Australian Longitudinal Study of Aging (ALSA)	1992	8	1,403	55% men	> 70
Bell et al., 2014	USA/ Honolulu Heart Program (HHP)	1991 – 1993	up to 21	1,292	100% men	71-82
Britton et al., 2008	England/ Whitehall II study	1985 – 1988	17	5,823	71% men	35-55
Burke et al., 2001	USA/ Cardiovascular Health Study (CHS)	1989 - 1990, 1992 - 1993	6.5 and 3.5	3,342	39% men	> 65
Ford et al., 2000	USA	1993	2	602	33% men	> 70
Gu et al., 2009	China/ Chinese Longitudinal Healthy Longevity Survey (CLHLS)	2002	3	15,972	45% men	65-109
Gureje et al., 2014	Nigeria/ Ibadan Study of Ageing (ISA)	Aug 2003 - Nov 2004	64 months	930	61% men	> 65
Hamer et al., 2013	England/ English Longitudinal Study of Ageing (ELSA)	2002 – 2003	8	3,454	42% men	63.7
Hodge, English et al., 2013	Australia/ Melbourne Collaborative Cohort Study	1990 – 1994	11.7	5,512	37% men	63
Hodge, O'Dea et al., 2013	Australia/ Melbourne Collaborative Cohort Study	1990 – 1994	11.1 (wm)	6,309	39% men	64.1 (wm)
Kaplan et al., 2008	Canada/ Canadian National Population Health Survey (NPHS)	1994 – 1995	10	2,432	44% men	65-85
LaCroix et al., 2016	USA/ Women's Health Initiative (WHI)	1993 – 1998	16	68,153	100% women	50-79, 68.9 (wm)
Li et al., 2001	China/ Shanghai Mental Health Centre	1987	5	3,024	43% men	67.34
Newman et al., 2003	USA/ Cardiovascular Health Study (CHS)	1989 - 1990, 1992 - 1993	8	2,932	39% men	> 65, 71.9(wm)
Palmore, 1979	USA/ The First Duke Longitudinal Study	1955	21	155	46% men	60 - 74
Pruchno & Wilson-Genderson, 2014	USA/ ORANJ BOWL: Ongoing Research on Aging in New Jersey: Bettering Opportunities for Wellness in Life	2006 -2008	4	2,614	37% men	50-74, 60.53 (wm)
Sabia et al., 2012	England/ Whitehall II study	1991 – 1994	>16.3(median)	5,100	71% men	42-63, 51.3(m)
Shields & Martel, 2006	Canada/ National Population Health Survey (NPHS)	1994-1995	8	1,309	N/A	> 65
Sun et al., 2010	USA/ Nurses' Health Study (NHS)	1986	14	13,535	100% women	60 (m)
Tampubolon, 2016	England/ English Longitudinal Study of Ageing (ELSA)	2004	9	14,765	46% men	50-89
Terry et al., 2005	USA/ Framingham Heart Study (FHS)	1948-1971	45	2,531	44% men	40-50
Vaillant & Mukamal, 2001	USA/ Study of Adult Development at Harvard University	circa 1940	until 60 or death	724	100% men	born mainly in the 1920s

(m stands for mean, wm for weighted mean)

Table 2. Results of the eligible studies: associations of physical activity to healthy ageing

Study	Odds Ratio (95% CI) or b coef for Mixed Models	Sub-groups of adjustments
Almeida et al., 2013	RR, 95%CI Inactive at baseline, active at follow-up: 1.35, (1.17, 1.54). Active at baseline, inactive at follow-up: 1.07, (0.90, 1.30). Active at baseline and follow-up: 1.59, (1.36, 1.86). Inactive at baseline and follow-up: Reference.	Sociodemographic, Economic, Health Behaviour, Diseases & Physical Measurement
Andrews et al., 2002	OR, 95% CI Higher vs Intermediate level of function: None: Reference Moderate: 0.83, (0.58, 1.11) Vigorous: 0.47, (0.21-0.96) Higher vs Low level of function: None: Reference Moderate: 0.69, (0.48, 0.98) Vigorous: 0.81, (0.33, 1.46)	Sociodemographic, Economic
Bell et al., 2014	OR, 95%CI: Unhealthy vs Health Survival: 0.98, (0.75-1.28) PAI<=30.4: Reference	Sociodemographic
Britton et al., 2008	OR, 95%CI Men→ Vigorous: 1.9, (1.2-3.1), Not SEP adj: 2.4, (1.5-3.7) Moderate: 1.5, (0.9-2.4), Not SEP adj: 1.8, (1.1-2.8) None or mild: Ref Women→ Vigorous: 1.7, (1.1-2.6), Not SEP adj: 2.2, (1.5-3.7) Moderate: 1.4, (0.9-2.2), Not SEP adj: 1.7, (1.1-2.6) None or mild: Ref	Sociodemographic, Economic, Model
Burke et al., 2001	Proportion of HY: Model with Behavioural Factors only 1. no-exercise: Reference 2. Low: 1.30, 95%CI: (1.18, 1.98) 3. Medium: 1.37, 95%CI: N/A 4. High: 1.53, 95%CI: N/A Model with Behavioural Factors & Subclinical Disease Factors 1. no-exercise: Reference 2. Low: 1.25, 95%CI: (1.03, 1.52) 3. Medium: 1.34, 95%CI: (1.09, 1.64) 4. High: 1.42, 95%CI: (1.09, 1.85)	Sociodemographic, Economic, Health Behaviour, Diseases & Physical Measurements
Ford et al., 2000	OR, 95%CI: not exercise regularly: 1.01, (0.54, 1.89)	Sociodemographic, Economic, Health Behaviour, Diseases & Physical Measurements, Attitude & Social Environment

Gu et al., 2009	OR, 95% CI of access to healthcare at present & in childhood on healthy survival No: Reference Model I: 1.30, (1.15, 1.48) Model II: 1.12, (0.98, 1.28) Model III: 1.13, (0.99, 1.29)	Model I:Sociodemographic, Economic Model II: Sociodemographic, Economic, Attitude & Social Environment Model III: Sociodemographic, Economic, Attitude & Social Environment, Model Characteristics
Gureje et al., 2014	OR, 95%CI Total: Moderate: 1, (0.35, 2.61), Vigorous: 1, (0.40, 3.21) Male: Moderate: 0.9, (0.31, 2.42), Vigorous: 0.8, (0.27, 2.46) Female: Moderate: 1.2, (0.28, 5.25), Vigorous: 2.5, (0.33, 18.16)	Sociodemographic, Economic, Health Behaviour, Diseases & Physical Measurements, Attitude & Social Environment
Hamer et al., 2013	OR, 95% CI Inactive: reference Mod.: M1: 3.12, (2.30, 4.24), M2: 2.67, (1.95, 3.64) Vig.: M1: 4.35, (3.16, 5.98), M2: 3.53, (2.54, 4.89) Remained inactive: reference Became inactive: M1: 2.5, (1.27, 4.94), M2: 2.36, (1.19, 4.68) Became active: M1: 3.57, (1.79, 7.14), M2: 3.37, (1.67, 6.78) Remained active: M1: 9.51, (5.22, 17.33), M2: 7.68, (4.18, 14.09)	Model 1: Sociodemographic, Model 2: Sociodemographic, Economic, Health Behaviour
Hodge, English et al., 2013	OR, 95%CI Hi vs. lo physical activity:1.36, (1.18, 1.56)	Sociodemographic, Economic, Health Behaviour, Diseases & Physical Measurements, Attitude & Social Environment
Hodge, O'Dea et al., 2013	OR 95%CI Model with & without BMI and WHR: 1.44, (1.27, 1.64)	Sociodemographic, Economic, Diseases & Physical Measurements, Model Characteristics
Kaplan et al., 2008	OR 95%CI Thrivers vs NonThrivers: 1.08, (0.62, 1.88) Thrivers vs Deceased: 1.30, (0.72, 2.32)	Sociodemographic, Economic, Attitude & Social Environment, Health Behaviour, Diseases & Physical Measurements
LaCroix et al., 2016	OR, 95%CI Veterans, ≤9 MET-hrs/wk: 0.72, (0.60–0.86) Veterans, MET-hrs/wk, Adj.: 0.85 (0.70–1.03) Non-Veterans, ≤9 MET-hrs/wk: 0.69 (0.67–0.71) Non-Veterans, MET-hrs/wk, Adj: 0.82 (0.79–0.85) Model for Veterans Only: ≤10.5 MET-hrs/wk: 0.72 (0.61, 0.86) ≤10.5 MET-hrs/wk, Adj.: 0.85 (0.70, 1.03)	Crude: Sociodemographic, Economic Adj.: Sociodemographic, Economic, Model Characteristics, Health Behaviour, Diseases & Physical Measurements
Li, et al., 2001	OR,95%CI Work out, 1.1475, (1.0541 , 1.2492) RR, 95%CI Exercise regularly vs Little: 1.19, (1.10, 1.30) Seldom: 0.88, (0.81, 0.95) Sometimes: 0.99, (0.87, 1.14)	Sociodemographic, Health Behaviour

Newman et al., 2003	Proportion of SY for the Given Factor Compared with Someone without it Men, Women: <480, <320 : Reference 480-1069, 320-824 : 1.12 (0.97, 1.30) 1070-1835, 825-1440 : 1.19 (1.03, 1.37) 1836-3520, 1441-2625 : 1.11 (0.96, 1.28) >3520, >2625 : 1.27 (1.09, 1.47)	Sociodemographic, Economic, Diseases & Physical Measurements, Health Behaviour
Palmore, 1979	Slopes of Regression Analysis(B): Men: 0.026, Women: 0.057	Health Behaviour, Social Environment & Attitude
Pruchno & Wilson-Genderson, 2014	Successful: Reference Unsuccessful: b=-0.08, SD=0.06, 95%CI=(0.83, 1.03), exp(b)=0.92 Subjective only: b=-0.07, SD=0.05, 95%CI=(0.84, 1.04), exp(b)=0.94 Objective only: b=-0.10, SD=0.05, 95%CI=(0.82, 0.99), exp(b)=0.90	Sociodemographic, Economic, Health Behaviour, Social Environment & Attitude
Sabia et al., 2012	Successful Aging vs normal ageing or death OR, 95%CI Active: 1.45, (1.25, 1.68) Inactive: Reference	Sociodemographic, Economic, Health Behaviour
Shields, & Martel, 2006	Proportional HR, 95%CI: Frequent/ Occasional: 1.5, (1.1, 1.9) Infrequent: Reference	Sociodemographic, Economic, Diseases & Physical Measurements, Health Behaviour, Social Environment & Attitude

Sun et al., 2010	OR, 95%CI: Physical Activity, Quintiles (METs)-fully adjusted// age adjusted
	1.Median: 0.9. Ref
	2. Median: 3.6. 0.96, (0.78, 1.18) // 1.01, (0.83, 1.24)
	3. Median: 7.9. 1.30, (1.08, 1.57) // 1.53, (1.28, 1.84)
	4.Median: 16.2. 1.25, (1.03, 1.51) // 1.57, (1.31, 1.89)
	5. Median: 37.1. 1.76, (1.47, 2.12) // 2.39, (2.01, 2.85).
	Walking, Quintiles (METs)-fully adjusted // age adjusted
	1. Median: 0, Ref
	2. Median: 2. 0.99, (0.80, 1.22) // 1.04, (0.86, 1.28)
	3. Median: 3. 1.15, (0.94, 1.40) // 1.32, (1.09, 1.60)
	4.Median: 7.5. 1.42, (1.17, 1.72) // 1.82, (1.52, 2.18)
	5. Median: 20. 1.37, (1.10, 1.67) // 1.80, (1.50, 2.17)
		Sociodemographic, Economic, Diseases & Physical Measurements, Health Behaviour

Tampubolon, 2016	Baseline Model, Annual Rate of Phenotypic Decline: b: 0.240, 95%CI: (0.176, 0.303) Gender Interaction Model, Annual Rate of Phenotypic Decline: b: 0.237, 95%CI: (0.174, 0.301)	Sociodemographic, Economic, Health Behaviour, Diseases &Physical Measurements
Terry et al., 2005	Not statistically significant to predict survival to age 85	Sociodemographic, Economic, Health Behaviour, Diseases &Physical Measurements
Vaillant & Mukamal, 2001	OR, 95%CI : Happy-Well Men vs Sad-Sick or Prematurely Dead College Men at Age 75–80: 3.09, (1.30, 9.75) Core-City Men at Age 65–70: OR:-	Sociodemographic, Diseases & Physical Measurement, Health Behaviour, Attitude & Social Environment

(RR: Risk Ratio, HR: Hazard Ratio, HY: Healthy Years, SY: Successful Years)

Table 3. Summary of sensitivity and sub-group analysis

Analysis	No of Studies	ES	Lower Limit	Upper Limit	p-value	Heterogeneity	Trim & fill effect size	Lower Limit	Upper Limit	No of filled studies
Main Analysis	17	1.39	1.23	1.57	<0.001	81.10%	1.27	1.11	1.45	20
all reported statistics	21	1.38	1.25	1.52	<0.001	77.10%	1.26	1.13	1.41	25
				Sensitivity Analysis						
Low Risk of Bias	12	1.43	1.22	1.68	<0.001	84.70%	1.28	1.07	1.53	14
				Subgroup Analysis						
Disability&Disease&Mental Status in HA										
Yes	8	1.61	1.35	1.93	<0.001	82.90%	1.43	1.17	1.76	10
No	9	1.14	1.07	1.20	<0.001	0.00%	1.13	1.07	1.20	10
Physical Activity										
dichotomous var	10	1.26	1.15	1.38	<0.001	59.00%		data unchanged		-
no dichotomous var	7	1.68	1.17	2.41	0.005	90.00%	1.31	0.90	1.90	9
Physical Activity & Exercise										
Physical Activity	10	1.46	1.23	1.72	<0.001	80.60%		data unchanged		-
Exercise	7	1.20	1.07	1.34	0.002	51.00%	1.13	0.98	1.30	10
Age										
< 65y at the baseline	9	1.64	1.36	1.98	<0.001	87.30%	1.33	1.09	1.62	13
>=65y at the baseline	8	1.14	1.07	1.22	<0.001	0.00%		data unchanged		
Follow-Up (years)										
0-10	9	1.39	1.13	1.70	0.002	87.50%		data unchanged		-
>10	8	1.37	1.23	1.53	<0.001	47.80%	1.34	1.19	1.50	10
Main Analysis (less adjusted models)										
less adjusted models	17	1.51	1.30	1.77	<0.001	89.20%	1.37	1.16	1.63	19

Table 4. Meta-regression of effects modifiers of physical activity on healthy ageing

Response	Modifier	β	Lower Limit	Upper Limit	p-value	R^2	I^2 res	τ^2
Log(OR)	Biomedical Models	0.316	0.018	0.613	0.039	35.68%	67.42%	0.048
	65 yo and over at baseline	-0.369	-0.665	-0.072	0.018	31.66%	76.75%	0.051
	Binary var for activities	-0.292	-0.617	0.033	0.074	22.91%	81.73%	0.058
	Exercise vs Physical Activity	-0.080	-0.440	0.280	0.644	-3.14%	74.46%	0.077
	FollowUp (>10 y)	0.028	-0.327	0.383	0.871	-11.69%	80.56%	0.084